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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,084	HOOYKAAS ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 23* is/are pending in the application.

4a) Of the above claim(s) *3,6,8,9,13-15 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7,10-12 and 16-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/03,7/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 6/20/2003, in which claim 22 was canceled, claims 3-5, 9-12 and 15-21 were amended, and claim 23 was newly added. Receipt is also acknowledged of an amendment, filed 7/27/2006, in which claim 10 was amended. Currently, claims 1-21 and 23 are pending.

Election/Restrictions

Applicant's election without traverse of "providing a mutant of a component involved in nonhomologous recombination" as the species of method step, "ku70" as the species of component, and "fungus" as the species of eukaryote in the reply filed on 7/27/2006 is acknowledged. The response indicates that claims 1, 2, 4, 5, 7, 10-13 and 15-21 are readable on the elected species. However, claim 13 is drawn to the method step of "inhibiting a component involved in nonhomologous recombination," which does not read on the elected species of "providing a mutant of a component involved in nonhomologous recombination." Rather, the method step of claim 13 reads on the non-elected method step of claim 3. Claim 15 depends from claim 13 and thus reads on a non-elected species. Furthermore, it is noted that "fungus" and "yeast" are not patentably distinct, as yeast is a species of the genus of fungi. Thus, both "yeast" and "fungus" are under consideration.

Claims 3, 6, 8, 9, 13-15 and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/27/2006.

An examination on the merits of claims 1, 2, 4, 5, 7, 10-12 and 16-21 follows.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the European Patent Office on 12/22/2000. It is noted, however, that applicant has not filed a certified copy of the 00204693.6 application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

Receipt of information disclosure statements, filed on 6/20/2003 and 7/24/2003, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: parts 3A and 3B of Figure 3 are not separately described in the specification. Figure 3B appears to be a continuation of the alignment shown in Figure 3A. It would be remedial to remove the references to parts A and B, as Figure 3 is completely described as a single figure in paragraph [0022] of the specification. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either

"Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See paragraphs [0020], [0030], [0035] and [0043].

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 5, 7, 11, 12 and 16-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of the phrase "in a eukaryote with a preference for non homologous recombination" are unclear. The instant specification states, "Most (higher) eukaryotes do not, or at least not significantly, practice homologous recombination, although the essential proteins to accomplish such a process are available." See page 4, paragraph [0008]). The prior art teaches that, in yeast, homologous recombination is prominent in repair of double strand breaks (DSBs), whereas the non-homologous recombination

pathway is often considered as the main pathway for DSB repair in mammalian cells (e.g. Delacote et al, Nucleic Acids Research, Vol. 30, No. 15, pages 3454-3463, 2002; e.g. paragraph bridging pages 3454-3455). Further, van Attikum et al (The EMBO Journal, Vol. 20, No. 22, pages 6550-6558, Nov. 15, 2001, cited on the IDS filed 6/20/2003) teach that T-DNA transfer occurs by homologous recombination in yeast when the T-DNA carries homology with the yeast genome, whereas T-DNA transfer in plants integrates mainly by nonhomologous recombination in plants even when extensive homology is present (e.g. page 6550, right column, 2nd full paragraph). Thus, yeast are recognized in the art as having a preference for homologous recombination. This is consistent with the reference to "higher eukaryotes" in the instant specification. However, claim 10 limits the eukaryotic cell to a yeast or fungus cell. Accordingly, the metes and bounds of the eukaryotic cells encompassed by the claims are unclear. Moreover the claim is vague and indefinite in that the preamble recites, "directing integration of a nucleic acid of interest to a predetermined site, however the only method step recited in the claim is "steering an integration pathway towards homologous recombination." It is not clear that the claimed generic method step or even a species such as "providing a mutant of a component involved in nonhomologous recombination" *necessarily* result in directing integration of a nucleic acid, as there are no claimed positive action method steps that require a nucleic acid. Therefore, it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s).

Claims 2, 4, 5, 11, 12 and 16-21 depend from claim 1 and are indefinite for the same reasons applied to claim 1.

Claim 7 is vague and indefinite in that the metes and bounds of the claimed method are unclear. The preamble recites "A method of directing integration of a nucleic acid of interest to a subtelomeric region, a telomeric region, or a subtelomeric region and a telomeric region in a eukaryote." However, it is not clear that practicing the claimed method step of "providing a mutant of a component involved in nonhomologous recombination" will *necessarily* result in the integration of a nucleic acid to the regions recited in the preamble. The nucleic acid recited in the preamble is not used in any of the positive action method steps. Thus, it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 10-12 and 16-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for steering an integration pathway towards homologous recombination in a eukaryotic cell *in vitro* by providing a mutant component of nonhomologous recombination, does not reasonably provide enablement to steer an integration pathway towards homologous recombination in a eukaryotic cell *in vivo* and does not provide enablement for transient inhibition of integration via nonhomologous recombination by providing a mutant component involved in nonhomologous recombination. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to a method of directing integration of a nucleic acid of interest to a predetermined site, wherein said nucleic acid has homology at or around said predetermined site, in a eukaryote with a preference for nonhomologous recombination. The preamble of independent claim 1 reads on the integration of a nucleic acid of interest into a eukaryotic cell *in vitro* or *in vivo* (i.e. gene therapy).

The nature of the subject matter is complex, because the nucleic acid must be delivered at a level sufficient to produce a therapeutic outcome (see the discussion below).

Breadth of the claims: The claims encompass the use of the claimed method in any eukaryotic cell of any organism. Further, the claims are drawn to the integration of any nucleic acid at any site in the genome. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification envisions the use of the claimed method to deliver a gene to a eukaryotic cell *in vivo* (e.g. page 6). The specification envisions replacing a defective p53 with an intact p53 such that the tumoricidal gene is delivered to a predetermined site only in proliferating cells or tumor cells (e.g. page 6; paragraph bridging pages 11-12). Further, the specification envisions the delivery of a therapeutic proteinaceous substance by integration of a nucleic acid into a eukaryotic cell

(i.e. gene therapy) (e.g. paragraph bridging pages 11-12). Thus, the specification envisions the treatment of cancer and genetic diseases such as diseases that result from the expression of a defective protein product.

The specification provides little or no guidance with regard to gene therapy applications. All of the working examples of the specification are directed to the integration of DNA by homologous or nonhomologous recombination in *Saccharomyces cerevisiae* comprising stable mutations in components involved in nonhomologous recombination. The stable cell lines do not allow transient inhibition of nonhomologous recombination.

State of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J. Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al (1997) indicate that most approaches suffer from poor efficiency and transient expression of the gene (e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1 and 2). The post filing art indicates that still suffer from inefficient gene transfer (Verma and Weitzman, Gene Therapy: Twenty-first century medicine. Annual Review of Biochemistry, Vol. 2005, Vol. 74, pages 711-738, 2005; e.g. page712, last paragraph). Regarding viral methods for gene delivery *in vivo*,

Verma et al (1997), indicate that lentiviral, adenoviral and AAV vectors are capable of delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2).

Predictability of the art: The area of the invention is unpredictable. As discussed above, the method of *in vivo* gene therapy is highly complex and unpredictable. Indeed, recent gene therapy protocols have demonstrated unpredictable outcomes resulting from an unexpected inflammatory reaction to an adenoviral vector in a patient and the insertional mutagenesis of a gene resulting in a leukemia-like condition in children being treated for severe combined immunodeficiency (Edelstein et al, J. Gene Med. Vol. 6, pages 597-602, 2004; e.g. page 599, The hopes and the setbacks; Verma and Weitzman, pages 729-732, Clinical Trials: Successes and setbacks). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Gene therapy is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique (e.g. Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al, p. 33, col. 1, 1st paragraph; Verma and Weitzman, page 732, 2nd full paragraph).

Furthermore, it would be unpredictable to use a stable mutant cell line to transiently inhibit homologous recombination. The working examples of the specification teach that the inhibition is constant characteristic of the cells.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the claimed methods. With any nucleic acid

one would have to determine how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1, 2, 4, 5, 10-12 and 16-21 are not considered to be fully enabled by the instant specification.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for directing integration of a nucleic acid of interest to a subtelomeric region, a telomeric region, or a subtelomeric and telomeric region in *Saccharomyces cerevisiae* comprising providing a strain of *S. cerevisiae* comprising a mutation in component involved in nonhomologous recombination, wherein the component involved in nonhomologous recombination is selected from the group consisting of *rad50, mre11* and *xrs2*, does not reasonably provide enablement for the use of any other eukaryotic cell or mutations in any other components of nonhomologous recombination. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the

existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is complex in that the eukaryotic cell must contain a mutation in a component involved in nonhomologous recombination but must be capable of performing nonhomologous recombination to direct the integration of a nucleic acid to a subtelomeric region, a telomeric region, or a subtelomeric and telomeric region.

Breadth of the claims: The claims are broad in that they encompass the use of any eukaryotic cell and any mutant component involved in nonhomologous recombination. The claimed method step is not limited to a eukaryotic cell containing a specific mutation, as it reads on the step of providing a mutant isolated protein. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches the disruption of *YKU70, LIG4, RAD50, RAD51* and *RAD52* (e.g. paragraph [0026]; Table 1). The specification teaches that the frequency of T-DNA integration by nonhomologous recombination in *rad50, mre11, xrs2, lig4 and sir4* mutants was reduced dramatically: 20- to more than 40-fold (e.g. paragraph [0041]; Table 2). The *YKU70,* also referred to as *ku70,* mutant did not provide any G418-resistant colonies from several cocultivation experiments (e.g. paragraph [0041]). Thus, the *ku70* mutant is completely defective in nonhomologous recombination and would be incapable of directing nonhomologous recombination to telomeric or subtelomeric regions. With regard to the distribution of integration sites for those mutants still capable of some nonhomologous recombination, the specification teaches that the *sir4* mutant

does not have a preference for telomeric or subtelomeric regions. The specification teaches that only the *rad50, mre11,* and *xrs2* mutants direct integration to telomeric or subtelomeric regions (e.g. Table 3).

Predictability and state of the art: It would be highly unpredictable to practice the claimed invention with the elected species, *ku70*, as the specification teaches that this mutant is incapable of performing nonhomologous recombination (e.g. paragraph [0041]). The *ku70* mutant would be incapable of directing nonhomologous recombination to telomeric or subtelomeric regions.

Furthermore, it would be unpredictable to extrapolate the results obtained in yeast to other species such as human, mouse and rat. The prior art teaches that, in yeast, homologous recombination is prominent in repair of double strand breaks (DSBs), whereas the non-homologous recombination pathway is often considered as the main pathway for DSB repair in mammalian cells (e.g. Delacote et al, Nucleic Acids Research, Vol. 30, No. 15, pages 3454-3463, 2002; e.g. paragraph bridging pages 3454-3455). Further, van Attikum et al (The EMBO Journal, Vol. 20, No. 22, pages 6550-6558, Nov. 15, 2001, cited on the IDS filed 6/20/2003) teach that T-DNA transfer occurs by homologous recombination in yeast when the T-DNA carries homology with the yeast genome, whereas T-DNA transfer in plants integrates mainly by nonhomologous recombination in plants even when extensive homology is present (e.g. page 6550, right column, 2nd full paragraph). Thus, the mammals and plants differ from yeast in terms of the frequency and types of recombinational events. Further, Jensen-Seaman et al (Genome Research, Vol. 14, pages 528-538, 2004) teach that recombination rates differ between humans, mouse and rat: humans have about twice as much recombination as mouse and rat, and the rate

of recombination in humans is reduced near the centromeres and elevated near the telomeres (e.g. page 528, paragraph bridging columns). Accordingly, it would be unpredictable to extrapolate the results obtained with *Saccharomyces cerevisiae* to other organisms.

Amount of experimentation necessary: Given the lack of guidance in the specification with regard to the effects of mutations of components of nonhomologous recombination on the integration sites of nonhomologous recombination events in species other than *Saccharomyces cerevisiae*, one would be required to perform additional experimentation to identify those components than can be mutated in a particular eukaryote to result in directing integration of a nucleic acid of interest to a subtelomeric region, a telomeric region, or a subtelomeric region and a telomeric region. The additional experimentation would require a large amount of inventive effort, because the effects of a particular mutation in a component of nonhomologous recombination are unpredictable with regard to ability to direct a nucleic acid to a telomeric or subtelomeric region by nonhomologous recombination.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claim 7 is not considered to be fully enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 10, 12 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Jackson et al (WO 98/30902 A1, published July 16, 1998; see the entire reference).

Jackson et al teach that Ku-associated DNA double-strand break repair (KDAR) can be inhibited to increase the efficiency of gene targeting and gene therapy (e.g. page 7, line 6; paragraph bridging pages 8-9). Jackson et al teach that two ways exist for repairing DNA double-strand breaks (DSBs): the first is through the process of illegitimate recombination (also known as DNA non-homologous end-joining or NHEJ), which is catalyzed by the KDAR system, and the second is the process of homologous recombination, whereby the damaged DNA molecule exchanges information with an undamaged DNA homologous partner DNA molecule (e.g. paragraph bridging pages 8-9). Jackson et al teach that the illegitimate pathway tends to predominate in mammalian cells, and inhibiting the KDAR system will make the proportion of DSBs repaired by homologous recombination increase and the efficiency of homologous gene targeting to a specific site will increase (e.g. paragraph bridging pages 8-9). Jackson et al teach different method steps to accomplish the steering of recombination to the homologous recombination pathway: (1) inhibition of the interaction between XRCC4 and DNA ligase IV or XRCCR and DNA-Pkcs/Ku, which would be transient, and (2) providing a mutant of a component involved in KDAR (i.e. a non-homologous recombination system (e.g. page 10, lines 17-35; page 76, line 17 to page 77, line 17; page 78, line 30 to page 81, line 15). Specifically, Jackson et al teach the step of providing a mutant lig4 gene in the haploid *Saccharomyces cerevisiae* yeast strain W303α, which is defective in non-homologous recombination but is capable of homologous recombination (e.g. page 76, line 17 to page 77, line 17).

Regarding claim 4, Jackson et al teach the step providing a mutant of Ku70 in a yeast strain and teach that Ku70 does not play a crucial role in the homologous recombination process (e.g. page 79, lines 12-24; page 81, lines 4-6).

Regarding claim 20, Jackson et al teach the integration of sequence into various loci of the yeast genome of a lig4 mutant to determine the ability of the cells to use the homologous recombination pathway (e.g. page 77, lines 10-17). The nucleic acid introduced into the specific site into the genome confers a desired property of being identifiable to determine the level of homologous recombination in the yeast strain.

Claims 1, 2, 5 and 17-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Liang et al (PNAS, Vol. 93, pages 8929-8933, 1996; see the entire reference).

Liang et al teach the claimed step of providing a mutant of Ku80, a component involved in nonhomologous recombination, in a CHO cell (*xrs-6* clones; e.g. Abstract; page 8929, paragraph bridging columns). Liang et al teach the introduction of a 3' neo sequence to correct a defect in a 5' neo sequence, by introducing a pCMV-I-SceI plasmid into an *xrs-6* clone (e.g. pages 8931-8932, Gene Targeting in CHO-K1 and *xrs-6* cells). The 3' neo sequence replaces a portion of the 5' neo sequence to replace an inactive gene and provide antibiotic resistance, where the antibiotic resistance is a desired property that allows the cell to survive as a result of the encoded therapeutic proteinaceous substance (e.g. pages 8931-8932, Gene Targeting in CHO-K1 and *xrs-6* cells; Figure 3). The neomycin nucleic acid sequence of interest is part of a plasmid gene delivery vehicle (e.g. pages 8931-8932, Gene Targeting in CHO-K1 and *xrs-6* cells; page 8929, DNA Constructions).

Claims 1, 2, 7 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsukamoto et al (Genetics, Vol. 142, pages 283-391, February 1996, cited on the IDS filed 6/20/2003; see the entire reference).

Regarding claims 1, 2 and 10, Tsukamoto et al teach the step of providing a *Saccharomyces cerevisiae* mutant of a component involved in nonhomologous recombination, where the component is *rad50, mre11* or *xrs2* (e.g. paragraph bridging pages 386-387). The teachings of Tsukamoto et al anticipated the claimed method step and the eukaryote is a yeast.

Regarding claim 7, Tsukamoto et al teach the claimed method step of providing a *Saccharomyces cerevisiae* mutant of a component involved in nonhomologous recombination, where the component is *rad50, mre11* or *xrs2* (e.g. paragraph bridging pages 386-387). The teachings of Tsukamoto et al anticipate the claim, because Tsukamoto et al teach the claimed method step. Further, the specification teaches that mutation of *rad50, mre11* or *xrs2* in *Saccharomyces cerevisiae* results in the integration of a nucleic acid of interest to a subtelomeric region, a telomeric region, or a subtelomeric region and telomeric region (e.g. paragraph [0047] and Table 3). Thus, the teachings of Tsukamoto et al necessarily meet each of the limitations of claim 7.

Claims 1, 2, 7 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Moore et al (Molecular and Cellular Biology, Vol. 16, No. 5, pages 2164-2173, May 1996; see the entire reference).

Regarding claims 1, 2 and 10, Moore et al teach the step of providing a *Saccharomyces cerevisiae* mutant of a component involved in nonhomologous recombination, where the component is *xrs2* or *mre11* (e.g. pages 2168-2169, One class of NHEJ repair is dependent on *RAD50, XRS2* and *MRE11*; Table 4). The teachings of Moore et al anticipate the claimed method step and the eukaryote is a yeast.

Regarding claim 7, Moore et al teach the step of providing a *Saccharomyces cerevisiae* mutant of a component involved in nonhomologous recombination, where the component is *rad50, xrs2* or *mre11* (e.g. pages 2168-2169, One class of NHEJ repair is dependent on *RAD50, XRS2* and *MRE11*; Table 4). The teachings of Moore et al anticipate the claim, because Moore et al teach the claimed method step. Further, the specification teaches that mutation of *rad50, mre11* or *xrs2* in *Saccharomyces cerevisiae* results in the integration of a nucleic acid of interest to a subtelomeric region, a telomeric region, or a subtelomeric region and telomeric region (e.g. paragraph [0047] and Table 3). Thus, the teachings of Moore et al necessarily meet each of the limitations of claim 7.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 11, 16 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jackson et al (WO 98/30902 A1, published July 16, 1998; see the entire reference) in view of Bundock et al (The EMBO Journal, Vol. 14, No. 13, pages 3206-3214, 1995, cited on the IDS filed 7/24/2003; see the entire reference).

The teachings of Jackson et al are described above and applied as before.

Jackson et al do not specifically teach the replacement of a sequence within a eukaryote to replace an active gene with an inactive gene, where the nucleic acid of interest is part of a gene delivery vehicle, and the delivery of a nucleic acid of interest is by *Agrobacterium*.

Bundock et al teach the introduction of a plasmid pRAL7100, comprising a URA3 selection gene surrounded by DNA derived from the flanking regions of the *Saccharomyces cerevisiae* PDA1 gene, by co-cultivating *S. cerevisiae* with *Agrobacterium tumefacients* comprising the plasmid (e.g. page 3209, Evidence for T-DNA integration into the yeast genome). A double crossover event results in the replacement of the active PDA1 sequence with a disrupted, inactive PDA1 sequence (e.g. page 3209, right column; Figure 4). Further, Bundock et al teach that the use of *Agrobacterium tumefacients* to deliver the plasmid results in higher efficiency of recombination as compared to results that would be obtained by standard methods such as electroporation (e.g. page 3209, right column, 1st full paragraph; Table II).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of inhibiting KDAR in a cell to increase the efficiency of gene targeting of Jackson et al to include the delivery of the nucleic acid by *Agrobacterium tumefacients* for the replacement of an active gene by an inactive gene contained within a plasmid as taught by Bundock et al because both Jackson et al and Bundock et al teach it is within the ordinary skill in the art to perform homologous recombination in *S. cerevisiae*.

One would have been motivated to make such a modification in order to receive the expected benefit of increased efficiency of homologous recombination by delivering the nucleic acid by *Agrobacterium tumefacients* as compared to electroporation as taught by Bundock et al. Further, one would be motivated to inactivate an active gene to be able to study the effects of gene inactivation on the *S. cerevisiae* phenotype. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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